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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61M 37/00	A1	(11) International Publication Number: WO 00/61216
		(43) International Publication Date: 19 October 2000 (19.10.00)

(21) International Application Number: PCT/US00/09577

(22) International Filing Date: 10 April 2000 (10.04.00)

(30) Priority Data:
09/289,289   9 April 1999 (09.04.99)   US

(63) Related by Continuation (CON) or Continuation-in-Part
(CIP) to Earlier Application
US   09/289,289 (CON)
Filed on   9 April 1999 (09.04.99)

(71) Applicants *(for all designated States except US)*: B.H.B.,
L.C. [US/US]; 1801 Aston Way, Chesterfield, MO 63005
(US). LIEBEL–FLARSHEIM COMPANY [US/US]; 2111
E. Galbraith Road, Cincinnati, OH 45215–6305 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BAE, Kyongtae, T.
[US/US]; 3 Fleetwood Drive, St. Louis, MO 63124 (US).
TRAN, Huy, Q. [US/US]; 9185 Wrenwood Lane, St.
Louis, MO 63144 (US). SMALL, James, R. [US/US]; 2845
Bahns, Beavercreek, OH 45434 (US).

(74) Agents: HAFERKAMP, Richard, E. et al.; Howell & Hafer-
kamp, L.C., Suite 1400, 7733 Forsyth Boulevard, St. Louis,
MO 63105–1817 (US).

(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB,
BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM,
DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH,
GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR,
IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the
claims and to be republished in the event of the receipt of
amendments.

(54) Title: CONTRAST INJECTOR FOR INJECTING A CONTRAST MEDIUM TO GENERATE PROLONGED UNIFORM VASCU-
LAR ENHANCEMENT

(57) Abstract

A contrast medium injector (20) for injecting a patient with contrast
medium for a CT scan is programmed to provide an injection protocol that
is a representation of an ideally defined exponential curve with an initial
injection rate decaying at an exponential rate. This has been found to produce
a uniform vascular enhancement for the scanning of a patient's blood vessels.
The particular exponential decay coefficient which has been found to be optimal
is directly proportional to the cardiac output divided by the patient's weight,
and is approximated at 0.01 for a typical human.

Contrast Injector For Injecting A Contrast Medium To Generate
Prolonged Uniform Vascular Enhancement

Background of the Invention

One of the inventors herein is also the inventor of several
prior patents related to the improved enhancement of a patient's
organ undergoing a computed tomographic scan by controlling the
5   injection of a contrast medium in accordance with a predicted
enhancement. These patents include US Patents Number 5,583,902 and
5,687,208, the disclosures of which are incorporated herein by
reference. Still other patents have been issued relating to contrast
injectors and their use in order to obtain specific enhancement
10   levels. These include US Patents Number 5,827,219; 5,840,026;
5,383,858; 5,662,612; 5,681,286; 5,456,676; and 5,300,031; the
disclosures of which are incorporated herein by reference. Still
other patents which have been issued and which relate to the field of
contrast injectors and their use include US Patents Number 4,006,736;
15   5,868,710; 4,854,324; 4,210,138; 4,812,724; 5,865,744; 5,279,569;
5,865,805; 4,213,454; 4,695,271; 5,322,511; 5,269,762; and 5,851,184;
the disclosures of which are also incorporated herein by reference.

While the use of contrast injectors for injecting a patient
with a contrast agent in order to enhance a tissue or organ for CT
20   scanning has been done for years, the first two patents mentioned

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above, i.e. the '902 and the '208 patents, represent one of if not
the earliest attempt to scientifically solve the problem of computing
an expected enhancement based upon a patient's physical parameters,
assuming a given injection protocol. The inventors work in these
5 prior patents was directed at solving this problem for a patient's
organs, using complex differential equations and their solutions to
help answer how a human body functions in processing the contrast
agent, and then calculating a window of enhancement for which the
threshold of desired enhancement is exceeded for a successful scan,
10 assuming a typical injection protocol. As part of the '208 patent,
CT angiography was described and its special problems in obtaining
high quality scans of blood vessels.

CT angiography (CTA) has been widely accepted, in some cases
preferred over conventional angiography, to evaluate the anatomy of
15 major blood vessels such as the aorta and pulmonary artery. In the
prior art, the vessels are scanned using a thin-collimation spiral CT
technique, while a bolus of contrast medium is injected at a high
injection rate (3-5 mL/s) to achieve a high degree of vascular
contrast enhancement. Typically, contrast medium is injected at a
20 constant injection rate, i.e. a uniphasic injection protocol is used.
This injection scheme results in a steadily rising vascular contrast
enhancement profile with a single peak of enhancement occurring
shortly after the completion of the injection, as shown by the data
collected from a porcine experiment as shown in fig. 1a.
25 Consequently, vascular enhancement tends to be non-uniform during
image acquisition.

Uniform vascular enhancement through the entire period of
image acquisition is highly desirable for the purpose of image
processing and display, in which 3D postprocessing is frequently
30 based on a threshold CT attenuation value. In addition, it is
expected that uniform enhancement would contribute to an optimized
usage of contrast medium. In other words, for a given volume of
contrast medium, a uniform contrast enhancement whose magnitude is
lower than that of a peak enhancement generated by a uniphasic
35 injection would provide a longer temporal window of adequate vascular
enhancement than the uniphasic injection presently used in the prior
art, thereby resulting in a longer optimal scanning interval.
Alternately, it is expected that a smaller volume of contrast medium
would be needed to provide a uniform vascular enhancement for the

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same scanning duration as that achieved by using a uniphasic injection protocol.

In addition to a uniphasic injection protocol, a biphasic injection protocol is sometimes used as well in the prior art. A

5   typical biphasic injection protocol consists of two phases: a short rapid-injection phase, followed by a longer slow-injection phase. A biphasic injection protocol yields more prolonged enhancement than a uniphasic injection protocol, but it generates two enhancement peaks with a valley of enhancement in between. Data collected from another

10 porcine experiment as shown in fig. 1b supports this conclusion. Each peak occurs shortly after the completion of each injection phase, as might be expected given the results from the first porcine experiment. Although the biphasic might be considered by one less sophisticated as a step in the right direction, it actually increases

15 the complexity of the problem of first of all achieving a level of enhancement which reliably exceeds a threshold and then maintaining an enhancement level above that threshold for a time period that will be adequate to collect the image. As the prior art has little to teach with respect to solving this problem, other than the inventors

20 own work which has not yet focussed on the injection protocol aspect of the problem, it would seem that unguided use of a biphasic injection protocol would perhaps increase the amount of contrast agent injected needed to reliably achieve a successful scan over that of a simple uniphasic injection protocol whose enhancement is easier

25 to predict.

The present invention carries the inventor's prior work further by focussing on the injection protocol for CT angiography of the vascular system of a patient, and more particularly by computing an optimum solution of a specific contrast injection protocol for

30 optimizing both the level of enhancement as well as the temporal duration of the enhancement, and an injector to achieve such injection protocol. A byproduct of this invention is as before, the ability to minimize the amount of contrast agent needed to be injected into a patient in order to reliably obtain a successful

35 scan. This is important not only from a cost standpoint as the contrast agent can be expensive, but also from a health standpoint for the patient. The smaller the amount of contrast agent injected into a patient's body the less risk of harmful side effects.

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More particularly, the inventors herein have succeeded in developing a contrast injector and a contrast injector protocol for implementation in the contrast injector which optimizes the use of the contrast agent to reliably achieve an enhancement in excess of a

5   preselected threshold and to maintain that "excess" level of enhancement for a temporal duration that is near optimal given the amount of contrast agent used. The contrast injection protocol comprises a ramped, or multiphasic, or exponentially decaying, or steadily decreasing injection rate. An ideal solution is provided by

10   the solution of differential equations describing a simplified compartment model in lieu of the more complex whole body model taught in one of the inventors prior patents mentioned above. This solution renders an exponentially decaying rate of injection having a particular decay coefficient. However, it is contemplated that in

15   the real world, this exponentially decaying injection rate could be approximated by a linearly decay, or ramped decay, or even multi-step decay and yet yield acceptable results in accordance with the teachings of the present invention. Indeed, in the real world, something less than a true exponentially decaying injection rate must

20   necessarily be the physical limit of a contrast injector, even the computer programmable one taught herein as part of the invention. Perhaps even more so as the computer programmable injector uses digital control which in actuality is a series of relatively small steps in changing the injection rate. Still another factor to

25   consider and which also minimizes the precision that might be thought necessary is the varying physiological response between different patients to the injected contrast agent. As such, mathematical precision is not considered as a limit to the present invention.

The particular exponential decay coefficient calculated is

30   proportional to the cardiac output per body weight of the patient. Experimental data with pigs suggests that a decay coefficient of approximately 0.01 would be appropriate for humans. In order to render the injector easier to implement for a typical attending professional, the cardiac output of the patient could be assumed in

35   advance as average and thus no patient specific input need be made in order to achieve an acceptable scan. The experimental data suggested that the decay coefficient designed to generate a uniform enhancement for normal cardiac output resulted in a more dome-shaped enhancement with an increased magnitude for a subject with impaired cardiac

output, demonstrating the effect of cardiac output on contrast enhancement. In theory, albeit difficult in the real world, if the degree of cardiac output reduction is known, the exact same uniform vascular enhancement can be reproduced for patients with reduced

5   cardiac output. This can be achieved by lowering the initial injection rate and decay coefficient calculated for patients with normal cardiac output, proportional to the reduction in cardiac output. However, it is apparent that a multiphasic injection protocol designed to achieve a certain level of vascular enhancement

10   in patients with normal cardiac output will not result in overestimation of contrast medium enhancement in patients with reduced cardiac output. The term multiphasic is intended to refer to the injection protocol which is the subject of the present invention. It is to be distinguished from the simple uniphasic or biphasic

15   protocols of the prior art, and represents a protocol which is variable over time in a decreasing fashion whether continuously or discontinuously, ramped, linear, curvilinear, or intermittently.

        The duration of aortic enhancement can be prolonged either by increasing the volume of contrast medium for a given initial

20   injection rate or by injecting slowly at a lower initial rate for a given contrast medium volume. With a uniphasic injection, peak magnitude of aortic enhancement depends on three injection factors, i.e. the concentration, injection rate, and total volume of contrast medium. With a multiphasic injection protocol, however, the peak

25   magnitude can be independent of the total volume of contrast medium, provided that the volume is not too small to reach an initial upslope enhancement to a plateau or threshold level. Thus, multiphasic injection is advantageous over uniphasic injection when a prolonged duration is desired, while keeping contrast enhancement from rising,

30   by increasing the volume of contrast medium. Using the teachings of the present invention, this multiphasic injection protocol represents the ideal protocol to reliably achieve a uniform enhancement in excess of a threshold value for a desired temporal window as necessary for a vascular scan.

35   While the principal advantages and features of the present invention have been briefly explained, a fuller understanding of the invention may be gained by referring to the drawings and the detailed description of the preferred embodiment which follows.

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Brief Description of the Drawings

Figures 1a and 1b are graphs of empiric time-enhancement curves
from a 25kg pig using (a) uniphasic and (b) biphasic injections;

Figure 2 is a block diagram depicting a compartment model for
5 early pharmacokinetics of contrast enhancement;

Figure 3 is a graph of three multiphasic injection profiles
with the initial injection rate of 2 mL/s and different exponential
decay constants;

Figure 4 is a graph of a simulated porcine aortic enhancement
10 curve;

Figures 5a and 5b are graphs of three exponential injections
and their corresponding simulated porcine aortic contrast
enhancements;

Figure 6 is a graph of a simulated aortic contrast enhancement
15 curve in a human model with uniphasic and multiphasic exponential
injections;

Figure 7 is a series of simulated aortic contrast enhancement
curves in a human model with normal and reduced cardiac outputs;

Figures 8a and 8b are empiric porcine aortic enhancement curves
20 using multiphasic exponential injections in a 25 kg pig and a 40 kg
pig;

Figures 9a and 9b are graphs of the empiric porcine aortic
enhancement with uniphasic and multiphasic injections of 50 mL and 70
mL contrast medium;

25 Figures 10a and 10b are graphs of empiric porcine aortic
enhancement curves generated by various injections with 90 mL and 70
mL contrast medium; and

Figure 11 is a perspective view of a contrast injector
programmed to provide multiphasic injections.
30

Detailed Description of the Preferred Embodiment

Now will be explained the methodology for calculating the
multiphasic solution for achieving a uniform vascular enhancement.

The distribution of contrast medium in a blood vessel depends
35 on the circulating blood flow and blood volume of the vessel.
Although a whole body model provides a complete description of
enhancement characteristic in each vessel and each organ, modeling
with a limited number of compartments is less complex and more
approachable for theoretical analysis of various injection

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parameters. There are various ways to model body compartments. An optimal model is the one that uses the smallest number of compartments, but adequately describes the underlying pharmacokinetic process. An approach frequently used in prior art studies of drug

5   distribution is to model the whole body with two compartments, whereby contrast medium is introduced into a central plasma compartment, distributed to a peripheral extracellular compartment, and then eliminated from the central plasma compartment by renal excretion. Although this scheme is sufficient for describing the

10 late pharmacokinetics of contrast medium (hours), it needs further refinement to be applied to the description of early pharmacokinetics (minutes).

Figure 2 shows a compartment model which is designed to simulate early contrast enhancement in the aorta. In this model,

15 contrast medium is injected into the antecubital vein and distributed to the right heart, the pulmonary compartment, the left heart, and the aorta. It then recirculates back to the right heart via the systemic circulation. This transport scheme is specifically simplified to focus on early pharmacokinetics of the aortic contrast

20 enhancement, thus reducing the complexity of our analysis. For example, a constant elimination of contrast medium from the central blood compartment by renal excretion (transport to urine) is only substantial in late pharmacokinetics and thus not considered in this simple compartment model.

25 The model in Figure 2 is described mathematically as follows. Let Cv, Cr, Cp, Cl, and Cs be the contrast concentrations in the peripheral vein (from the antecubital to the right heart), right heart, pulmonary, left heart, and systemic circulation, respectively. Vv, Vr, Vp, Vl and Vs represent the corresponding compartment (blood

30 and interstitial) volumes of the peripheral vein, right heart, pulmonary, left heart, and systemic circulation, respectively. Qv is the volumetric flow rate of blood leaving the peripheral vein. Qr, Qp, Ql, and Qs are equivalent and represent the cardiac output of the system. Cc and Qc are the concentration and volumetric flow rate of

35 injected contrast medium, respectively. During contrast injection, all the volumetric blood flow rates (Qv, Qr, Qp, Ql, and Qs) are increased by Qc. The governing equations for the model are written from mass balance equations for each compartment (Equations 1-5 in Appendix A).

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The aortic enhancement curves were computer simulated by
numerically solving Equations 1-6 in Appendix A. The physiological
parameters used in the model for humans include 40 mL for Vv
(peripheral vein), 250 mL each for Vr (right heart) and for Vl (left
5   heart), 600 mL for Vp (pulmonary circulation), and 10 L for Vs
(systemic circulation). Associated volumetric blood flow rates are
250 mL/min or 4.2 mL/sec for Qv and 6.5 L/min for the cardiac output.
These values were estimated based on published human physiology data
for a standard adult. To mimic channels of blood vessels, the
10 peripheral venous compartment and pulmonary compartment are further
divided into multiple smaller compartments in series (5
subcompartments for the peripheral venous compartment and 30
subcompartments for the pulmonary compartment).

Since detailed cardiovascular physiologic data for porcine
15 models are rather lacking compared to human models, the inventors
rescaled the above human physiological parameters to determine the
physiological parameters for the porcine model. The compartment
volumes of the porcine model were estimated by multiplying the
compartment volumes of a standard 70 kg human model by the body
20 weight ratio, e.g. for a 25 kg pig, the ratio is 25:70. It is known
that the average cardiac output per body weight of pigs is twice as
high as that of humans. Therefore, the cardiac output for a 25 kg
pig corresponds to that of a 50 kg human. Although there is some
subjectivity in selecting these parameters, they were estimated
25 within available physiologic data and represent simply a set of
reference values for simulation to compare with experimental data.

A total of 38 ordinary differential equations were used to
describe the model in Figure 2. These equations were solved using
numerical integration programs of fifth-order Runge-Kutta method.
30 This model was run at a personal computer and took less than a
fraction of a second to compute. The contrast concentration curve
over time was calculated for each region by solving these
differential equations for a given contrast injection protocol.
After the contrast concentration in each compartment was computed by
35 solving Equations 1-6, it was translated into a CT enhancement value.

For a given input injection protocol, the mathematical model
described above can be used to predict the output contrast
enhancement curve of the aorta. Conversely, the model can be used to
solve the inverse problem, i.e. to predict an input function for a

given output contrast enhancement profile. Solving for an input
contrast injection algorithm which will generate a prolonged, uniform
vascular contrast enhancement is the focus of the present invention.

The inverse problem can be solved directly by the Laplace
5   Transform of governing equations in the model with a given desired
constant aortic enhancement and initial conditions. Mathematical
manipulation for the solution is detailed in Appendix A. This
solution, i.e. a contrast injection profile, was in turn applied as
an input to the mathematical model to simulate and verify the
10 reproducibility of desired constant aortic contrast enhancement.
Simulation was performed for both porcine and human mathematical
models by adjusting the physiological input values. Different
injection profiles were tested to study how they affect aortic
contrast enhancement. In addition, the effect of reduced cardiac
15 output on the enhancement was investigated. The model was modified
by decreasing the cardiac output by 20% and 40%. Contrast
enhancements were simulated in this model with the input injection
which, when used in normal cardiac output, would produce a uniform
contrast enhancement. The patterns of these enhancements were
20 compared with that from normal cardiac output.

In order to test the mathematical solutions, a porcine study
was conducted. All animal care and procedures performed were
approved by the Institutional Animal Study Committee. Four pigs
weighing initially 24-26 kg underwent scanning in two or three
25 separate sessions. Each session was separated by at least two days.
Two pigs had all their sessions within a week, while the other two
pigs had their first two and last sessions delays 4-5 weeks, which
results in an increase in their weight to 35-40 kg in their last
session.

30   In each session, the pig was anesthetized, intubated, and
underwent scanning for three or four sets of images obtained in
random order. During scanning, each pig was ventilated with oxygen
and low tidal volume to minimize breathing motion artifact. Each
image set consisted of 27 dynamic CT sections (5 mm collimation)
35 acquired at a fixed mid-abdominal aortic level, following i.v.
injection of contrast medium into a peripheral vein. Each set of
scans were 45-60 minutes apart to minimize the effect of prior
contrast administration. All CT scanning was performed with a

Somatom Plus-S scanner (Siemens Medical Systems, Iselin, New Jersey) using a one-second scanning time and a one-second interscan delay.

Three types of injection schemes were tested: uniphasic, biphasic, and multiphasic. Biphasic injections were performed by a
5 prior art power injector which was used in routine clinical CT scanning while uniphasic and multiphasic injections were conducted with a power injector which was invented for achieving the required protocols. This power injector was capable of delivering contrast medium in various uniphasic or multiphasic injection algorithms, as
10 is explained in greater detail below. The multiphasic injection rate is determined by an initial injection rate and an exponential decay coefficient, as shown in Figure 3. The total injected volume of contrast medium corresponds to the integrated sum of the multiphasic injection over injection duration.

15 Most injections were performed with the initial injection rate of 2 mL/s. Volumes of contrast medium used were 50, 70 and 90 mL of iothalmate meglumine (Conray 60; Mallinckrodt Medical, St. Louis, Missouri; 282 mgI/mL). Three differential exponential decay coefficients (0.007, 0.017, 0.026) were tested. These coefficients
20 were initially designed as (0.01, 0.02, 0.03), respectively, until further testing and verification revealed discrepancies between the design and actual values. These were the three smallest discrete increments allowed in the prototype of the inventive power injector. Decay coefficient higher than 0.03 was not used because it was
25 evident that a further increase in the coefficient would deviate further away from uniform vascular enhancements. A uniphasic injection was determined as being equivalent to a zero exponential decay coefficient where the injection rate remains constant at an initial injection rate throughout the injection duration.

30 Most extensively tested and compared injections were 50 mL total of contrast medium injected by a uniphasic injection of 2 mL/s and by a multiphasic injection of 2 mL/s initial rate having an exponential decay coefficient of 0.017. The same injection methods were repeated but with an increased total contrast medium volume to
35 70 mL or with both increased injection rate to 3 mL/s and increased volume to 90 mL. Other injections studied include biphasic injections of 50 mL (2 mL/s for 12 sec and then 1.4 mL/s for 18 sec) and 70 mL of contrast medium mL (2 mL/s for 17 sec and then 1.0 mL/s for 36 sec). Approximately half of the total contrast volume was

injected in each phase of the biphasic injections. The first and second injection rate of the biphasic injections were determined by the initial and final injection rates of the multiphasic injections with an exponential decay coefficient 0.017 of a corresponding total

5   contrast medium volume, respectively.

Attenuation values of the aorta were measured from post-contrast scans (at the same level as the pre-contrast scans) using a circular region of interest (ROI) at the center of the aorta. Contrast enhancement was calculated as the absolute different in

10   attenuation value between the pre- and post-contrast scans. For the data analysis, the injection duration (ID), the magnitude of peak aortic enhancement (PA), and the uniformity of enhancement (the duration of the enhancement achieved with 90% of the peak: 90%DCE) were evaluated. Means and standard deviations were also computed.

15   The results are now explained.

Figure 4 shows a simulated aortic enhancement curve generated from the model for a 25 kg pig with 50 mL of 282 mgI/mL contrast medium injected at a uniphasic 2 mL/sec. This curve was in good agreement with an empiric aortic enhancement curve observed in a 25kg

20   pig A (Figure 1A), including the time to and the magnitude of the peak aortic enhancement (simulated vs. empiric: 28 vs. 26 sec and 234 vs. 250 HU). These curves differed notably at the after-peak portion when the recirculation of contrast becomes substantial with the discontinuity of contrast injection. This portion was simplified

25   in the model which mainly focused on the early part of the injection protocol, i.e. the first pass of contrast bolus pharmacokinetics.

The contrast injection algorithm that provided a uniform, prolonged vascular enhancement was solved as shown in Appendix A. The solution, i.e. contrast injection protocol is expressed as the

30   product of an initial rejection rate and an exponential function of time, as shown in Equation 15. The exponential decay coefficient equals Q/Vs, the ratio of the cardiac output to the systematic volume of distribution of contrast medium, which is itself proportional to the cardiac output per body weight.

35   Figure 5a shows three exponential injection profiles with a 2 mL/s initial injection rate and decay coefficients (0.01, 0.02, and 0.03) for a 120 sec injection duration. The total amount of contrast medium in each injection is represented by the area under each curve. A lower exponential decay resulted in a higher total amount of

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contrast medium and a higher final injection rate at 120 sec. Aortic
contrast enhancement curves corresponding to these exponential
injection profiles were simulated from the mathematical model (with
porcine physiological parameters) by solving Equations 1-6 and are
5   depicted in Figure 5b. Uniform, plateau aortic enhancement was
observed with an exponential decay constant of 0.02
($Q/Vs=77/3571=0.021$). With decay coefficients 0.01 or 0.03, contrast
enhancement either steadily rises above this plateau level or
declines after a peak below the plateau level, respectively.

10   Figure 6 shows two simulated aortic enhancement curves for a
human model using uniphasic or multiphasic injection protocols with
0.01 ($Q/Vs=108/10000$) exponential decay injections at an initial
injection rate of 3 mL/s for a total of 160 mL of contrast medium. A
prolonged, uniform contrast enhancement was achieved with the
15   multiphasic injection protocol. Notice that this exponential decay
coefficient for the human model is approximately half that of the
porcine model, reflecting the physiological values used in the model
that the average cardiac output per body weight for humans is half
that for pigs.

20   The effect of reduced cardiac output on the enhancement was
evaluated by reducing the cardiac output by 20 and 40% in the model.
The exponential injection with a decay coefficient 0.01, which
generates a uniform enhancement for normal cardiac output ($Q=108$
mL/s), was used as the input contrast injection to this model with
25   reduced cardiac output. The output simulated aortic enhancements are
shown in Figure 7. As shown therein, the contrast enhancement curves
become more dome-shaped with an increase in magnitude, as the cardiac
output decreases.

    Figure. 8 demonstrates the empiric porcine aortic enhancement
30   curves obtained for two pigs using multiphasic exponential injections
with three different exponential decay coefficients (0.007, 0.017,
0.026). The contrast injection profiles are described in Figure 3.
Exponential injection with a decay constant of 0.017 showed the
aortic enhancement to be more uniform than with other injection
35   protocols. This result was compatible with the theoretical model
prediction that an exponential injection with a decay constant of
0.02 provided a plateaued aortic enhancement. Injections with lower
(0.007) or higher (0.026) decay constant resulted in aortic
enhancements steadily rising or declining after a peak, respectively,

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as predicted by the theoretical model. The magnitude of aortic
enhancement in Figure 8a was substantially higher than that in Figure
8b, reflecting the difference in body weight between two pigs (25 kg
vs. 40 kg). However, the patterns of aortic enhancement produced by

5   three different exponential decay coefficients were consistent.

Aortic enhancement curves in two pigs experiencing uniphasic
and multiphasic exponential injections are shown in Figure 9 for (a)
50 mL and (b) 70 mL of contrast medium. The uniphasic injection used
a contrast injection rate of 2 mL/s, while the multiphasic injection

10   started at 2 mL/s but declined exponentially with a decay constant
0.017. The illustrated results clearly demonstrate that multiphasic
injections yielded more prolonged and uniform vascular enhancement
than uniphasic injections. Performance of the multiphasic compared
with the uniphasic injection can be summarized for four pigs as

15   follows. For a 2 mL/s initial injection rate of 50 mL contrast
medium, the multiphasic injection increased ID by 30%, reduced PA by
a mean of 19%, and increased 90%DCE by a mean of 81%. For 70 mL
injections with a 2 mL/s initial injection rate, ID increased by 51%,
PA decreased by 18%, and 90%DCE increased by 94%.

20   Figure 10a shows empiric aortic enhancement curves in a 40 kg
pig obtained with uniphasic and multiphasic exponential (decay
coefficient 0.017) injections with a 3 mL/s initial injection rate
and 90 mL of contrast medium. In this pig, the multiphasic injection
method resulted in more prolonged, uniform but slightly declining

25   aortic enhancement. Figure 10b demonstrates three empiric aortic
enhancement curves generated by uniphasic, multiphasic and biphasic
injections of 70 mL of contrast medium. The uniphasic injection
consisted of a 2 mL/s injection for 35 sec, while the multiphasic
injection had an initial rate of 2 mL/s with a decay coefficient of

30   0.017 for 53 sec. The biphasic injection was performed with a 2 mL/s
rate for 17 sec and then a 1.0 mL/s rate for 36 sec. Multiphasic
injections again yielded more prolonged and uniform vascular
enhancement than uniphasic injections. A biphasic injection resulted
in more prolonged enhancement than a uniphasic injection but

35   generated two enhancement peaks with a valley in between.

A prolonged, uniform vascular enhancement is desirable in CT
angiography and some chest CT applications where the vessels, not the
parenchyma of organs, are the target of interest. This enhancement
pattern is useful for the purpose of image processing and display, in

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which 3D postprocessing is frequently based on a threshold CT attenuation value. It may also provide a longer optimal scanning interval for a given volume of contrast medium than a single-peaked contrast enhancement generated by a conventional uniphasic injection.

5   Alternatively, it may enable the use of a lower volume of contrast material for a given scanning duration.

Prolonged, uniform aortic contrast enhancements can be achieved by multiphasic exponential injections with adequately selected decay coefficients in accordance with the teaching of the present

10   invention. The multiphasic injection protocol was mathematically derived from a physiologically-based pharmacokinetic model, and then a porcine model was used to confirm findings observed in theoretical analyses and computer simulations. Although further clinical studies are warranted to validate the findings and injector performance, it

15   is expected from previous experiences in comparative studies and pharmacokinetics that a human model would behave similarly.

A simplified compartment model which has a limited number of compartments, instead of a more complex whole body model was used. The current compartment model was designed specifically to solve for

20   a contrast injection profile which generates a prolonged, uniform vascular enhancement. This simple model does not provide a complete description of enhancement characteristics in each organ but can adequately describe the underlying pharmacokinetic process of interest, i.e. first-pass enhancement characteristics of the aorta.

25   In this respect, the simulated results correlated well with the experimental results from the porcine model. Since the model equations 1-5 in Appendix A do not include renal or other clearance from the systemic circulation, the contrast concentration maintains a steady plateau following the cessation of contrast injection. This

30   may not be a significant factor in scans of less than 5-10 min duration.

The fact that a multiphasic exponential injection generates a uniform vascular enhancement can be explained conceptually as follows. Contrast enhancement in a system is proportional to the net

35   amount of contrast medium present, i.e. inflow minus outflow contrast medium. Aortic enhancement reflects an accumulation of contrast medium in the central blood volume (i.e. contrast medium injected and recirculated minus medium diffused away from the vessel). Thus, vascular enhancement rises when the rate of contrast material

15

infusion into the central blood volume exceeds the rate at which contrast medium diffuses away. This physiological event explains that aortic enhancement peaks shortly after the completion of the injection with a uniphasic injection, representing the maximal

5 accumulation of contrast medium within the central blood volume compartment. The rate at which contrast medium leaves the central blood compartment to the interstitium compartment is likely proportional to the concentration gradient between the two compartments, i.e. an exponential function of time, because the

10 contrast transport phenomenon is governed by passive diffusion and permeability. Thus, when the outflow rate of contrast medium is balanced by the infusion rate of contrast medium by a multiphasic exponential injection protocol, a uniform vascular enhancement occurs.

15 The experimental results showed that proper selection of a decay coefficient in multiphasic exponential injections was crucial to generate uniform vascular enhancement. The decay coefficient was proportional to the cardiac output per body weight. Since the cardiac output per body weight in humans is half that of pigs, a 0.01

20 decay coefficient would be adequate for humans. This value, which is already normalized by body weight, is independent of body weight. For example, a multiphasic injection with a 0.017 decay coefficient resulted in a similar uniform vascular enhancement pattern but with a decrease in magnitude in the same pig scanned at its baseline weight

25 of 25 kg and later after gaining 15-20 kg.

The decay coefficient designed to generate a uniform enhancement for normal cardiac output resulted in more dome-shaped enhancement with increased magnitude when there is a reduced cardiac output, demonstrating the effect of cardiac output on contrast

30 enhancement. In theory, albeit difficult in practice, if the degree of cardiac output reduction is known, the exact same uniform vascular enhancement can be reproduced for patients with reduced cardiac output. This can be achieved by lowering the initial injection rate and decay coefficient calculated for patients with normal cardiac

35 output in an amount proportional to the reduction in cardiac output. However, it is apparent that a multiphasic injection designed to achieve a certain level of vascular enhancement in patients with normal cardiac output will not result in overestimation of contrast medium enhancement in patients with reduced cardiac output.

16

The duration of aortic enhancement can be prolonged either by increasing the volume of contrast medium for a given initial rejection rate or by injecting slowly at a lower initial rate for a given contrast medium volume. With a uniphasic injection, peak

5   magnitude of aortic enhancement depends on three injection factors, i.e. the concentration, injection rate, and total volume of contrast medium. With a multiphasic injection, however, the peak magnitude can be independent of the total volume of contrast medium, provided that the volume is not too small to reach an initial upslope

10   enhancement to a plateau level. Thus, a multiphasic injection protocol is advantageous over a uniphasic injection when a prolonged duration is desired, while keeping contrast enhancement from rising, by increasing the volume of contrast medium.

Although the theoretical analysis indicated that a multiphasic

15   injection should follow an exponential decay to generate a prolonged, uniform vascular enhancement, other functional patterns may be used to approximate an exponential decay. For example, a short segment of an exponential curve can be approximated by a linear function without much disparity. This implies in practice that a linear or ramped

20   injection protocol may be used instead of a strictly exponential injection when the injection duration is not too long and when the decay coefficient is relatively small (for example, the exponential curve with 0.007 decay coefficient in Figure 3). In addition, a subtle discrepancy in enhancement from a slightly different

25   approximation of exponential function may be indiscernible because of intrinsic physiological fluctuations in enhancement caused by vascular pulsation and respirator motion. However, these are all included as part of the present invention in accordance with the teaching herein.

30   The data demonstrates that biphasic injections were not sufficient to generate a uniform vascular enhancement. In the study, multiphasic injections were generated with subsecond temporal resolution by the prototype injector. However, this degree of high temporal resolution may not be necessary. The number and interval of

35   temporal steps required in multiphasic injection depends on the injection duration and exponential decay coefficients. Although the effect of temporal resolution on the enhancement produced by multiphasic injections has not been fully explored, multiphasic temporal resolution of 2-3 seconds appears sufficient to generate

uniform enhancement because of intrinsic physiological fluctuation. This factor presents another reason why strict adherence to all exponential decay function is not necessary in order to achieve clinically satisfactory and uniform vascular enhancement.

5   The particular contrast injector or delivery system which is thought by the inventors to be particularly useful for implementation of the present invention includes a computer, or other digitally programmable control, for providing operator input and control of the injection protocol. In particular, a Liebel-Flarsheim model CT 9000

10   ADV Contrast Delivery System, as depicted in fig. 11, represents such a contrast injector. As shown therein, the contrast delivery system 20 includes a power head 22 for accepting the syringe containing the contrast medium, a control console 24 which may be a LCD display to provide for operator input and control of the injector, and a stand

15   26 with a base 28 containing the computer or other digital controller.

       In the subject injector, the injection parameters are entered in phases. Each phase has a constant flow, a volume and an optional delay. These parameters are displayed on the injector control

20   console 24 and the operator can change the values. Typically, an operator can enter up to four phases. The injector then performs the injection by executing these phases in sequential order. For the injector of the present invention, the parameters of the 2nd phase were changed and the console screen redesigned to allow the operator

25   to enter the parameters for an injection with an exponentially decaying flow rate. The operator enters the exponential coefficient and an elapsed time in order to define the injection protocol. The initial flow rate for the 2nd phase is the flow rate of the 1st phase. This arrangement allows the operator flexibility to

30   experiment with different injection profiles that may include steady state flows before and/or after the exponential decaying flow. In the prototype injector, the 1st flow was used to allow the selected flow rate to reach steady state (approximately 2 mL of volume) and the 3rd phase was not used. The flow chart for, and the particular

35   software program used in, the prototype injector are included as Appendix B. Also included as part of Appendix B are the validation data which includes the data obtained by measuring during an injection the syringe volume versus time using a linear position transducer. A plot of this data is included, and compared with a

calculated graph of the exponential curve desired to be obtained. As shown, the actual result curve is a close approximation of the theoretical curve.

5 While the invention has been disclosed and described in the form of a preferred embodiment, the inventors contemplate that various changes and variations may be envisioned by those of ordinary skill in the art without departing from the invention. For example, the digital control and vagaries of actual devices may well result in injection protocols which are not truly exponential curves.

10 Furthermore, as mentioned above, other factors may serve to limit how close an injection rate may approximate an exponential curve. However, such variations are included within the teaching of the present invention as well as other modifications including changes to the particular injector. For example, virtually any logically

15 controlled injector would be able to perform a multiphasic injection protocol and the invention should not be considered to be limited to a computer controlled, or even a digitally controlled injector. While operator input is usually considered as desirable, a preprogrammed or instructed or wired injector which is set up to

20 perform a multiphasic injection protocol is also considered to be part of the present invention. Indeed, the invention should be considered as being limited only by the scope of the claims appended hereto, and their legal equivalents.

To develop governing equations for the model in Figure 2, mass balance

equations are written for each compartment with input and output contrast flow.

$$Vv \frac{dCv}{dt} = Qc(t)\, Cc \;-\; Qv\, Cv(t) \qquad\qquad [1]$$

$$Vr \frac{dCr}{dt} = Qv\, Cv(t) \;+\; Qs\, Cs(t) \;-\; Qr\, Cr(t) \qquad\qquad [2]$$

$$Vp \frac{dCp}{dt} = Qr\, Cr(t) \;-\; Qp\, Cp(t) \qquad\qquad [3]$$

$$Vl \frac{dCl}{dt} = Qp\, Cp(t) \;-\; Ql\, Cl(t) \qquad\qquad [4]$$

$$Vs \frac{dCs}{dt} = Ql\, Cl(t) \;-\; Qs\, Cs(t) \qquad\qquad [5]$$

subject to the initial conditions at time $t = 0$:

$$Cv(0) = 0,\ Cr(0) = 0,\ Cp(0) = 0,\ Cl(0) = 0,\ Cs(0) = 0 \qquad [6]$$

where $Cv(t)$, $Cr(t)$, $Cp(t)$, $Cl(t)$, and $Cs(t)$ represent the concentration of the contrast with

respect to time, t, within the peripheral venous, right heart, pulmonary, left heart (aorta),

and systemic compartments respectively. The Vv, Vr, Vp, Vl, and Vs are the volumes of

the various compartments which are assumed constant. These blood flow and volume of

each compartment are determined from known physiologic data. The Qv, Qr, Qp, Ql, and

Qs represent the flows. $Qc(t)$ and Cc are the time-dependent flow and concentration of the

injected contrast material. The flow in each compartment equals the cardiac output, Q:

$$Q = Qr = Qp = Ql = Qs.$$

20

Equations 1-6 can be numerically solved to predict and simulate an aortic enhancement curve for a given contrast injection condition. An example in a porcine model with 2 mL/s uniphasic injection is shown in Figure 4.

Conversely, these differential equations can be used to estimate an input contrast injection algorithm that generates a uniform, prolonged vascular enhancement, i.e. solving an inverse problem, as shown below. Because the initial contrast concentrations in the body compartments equal zero, taking the Laplace Transform of equations [1]-[5] yields

$$s \, (Vs \, \underline{Cv}(s)) = \underline{Qc}(s)Cc - Qv \, \underline{Cv}(s) \qquad [7]$$

$$s \, (Vr \, \underline{Cr}(s)) = Qv \, \underline{Cv}(s) + Q \, (\underline{Cs}(s) - \underline{Cr}(s)) \qquad [8]$$

$$s \, (Vp \, \underline{Cp}(s)) = Q \, (\underline{Cr}(s) - \underline{Cp}(s)) \qquad [9]$$

$$s \, (Vl \, \underline{Cl}(s)) = Q \, (\underline{Cp}(s) - \underline{Cl}(s)) \qquad [10]$$

$$s \, (Vs \, \underline{Cs}(s)) = Q \, (\underline{Cl}(s) - \underline{Cs}(s)) \qquad [11]$$

where $\underline{Cv}(s)$, $\underline{Cr}(s)$, $\underline{Cp}(s)$, $\underline{Cl}(s)$, $\underline{Cs}(s)$, and $\underline{Qc}(s)$ are the Laplace Transforms of Cv(t), Cr(t), Cp(t), Cl(t), Cs(t), and Qc(t) respectively. A uniform aortic enhancement profile, i.e. constant Cl(t), can be modeled effectively by letting

$$\underline{Cl}(s) = a \, \underline{H}(s) = \frac{\alpha}{s} \qquad [12]$$

where a is a scaling constant and $\underline{H}(s)$ is the Laplace Transform of the Heaviside step-function, H(t):

$$H(t) = \begin{cases} 0, & t < 0 \\ 1, & t \geq 0 \end{cases}$$

Combining [12] and [7]-[11],

21

$$Qc(s) = \frac{(sVv + Q)\alpha}{s\, Cc\, Qv} \left\{ \frac{(sVr + Q)\,(sVp + Q)\,(sVl + Q)}{Q^2} - \frac{Q^2}{(sVs + Q)} \right\} \qquad [13]$$

The inverse Laplace Transform of [13] gives the desired result:

$$Qc(t) = \frac{\alpha}{Cc\, Qv} \left\{ QQv - \frac{Q^2 Vv\, E^{\frac{-Qt}{Vs}}}{Vs} - \left(1 - E^{\frac{-Qt}{Vs}}\right) QQv + (QvVl + QvVp + QvVr + QVv)\delta(t) \right.$$

$$+ \left(\frac{(QvVlVp + QvVlVr + QvVpVr)}{Q} + VlVv + VpVv + VrVv \right)\delta'(t)$$

$$\left. + \left(\frac{QvVlVpVr}{Q} + VlVpVr + VlVrVv + VpVrVv \right)\frac{\delta^{(2)}(t)}{Q} + \frac{VlVpVrVv\, \delta^{(3)}(t)}{Q^2} \right\}. \qquad [14]$$

Equation [14] can be approximated by eliminating the terms involving the Dirac delta function, d(t), and its derivatives since these terms contribute only to the impulse rise in contrast concentration immediately following t = 0 and not to the steady-state behavior. Without these terms, [14] simplifies to
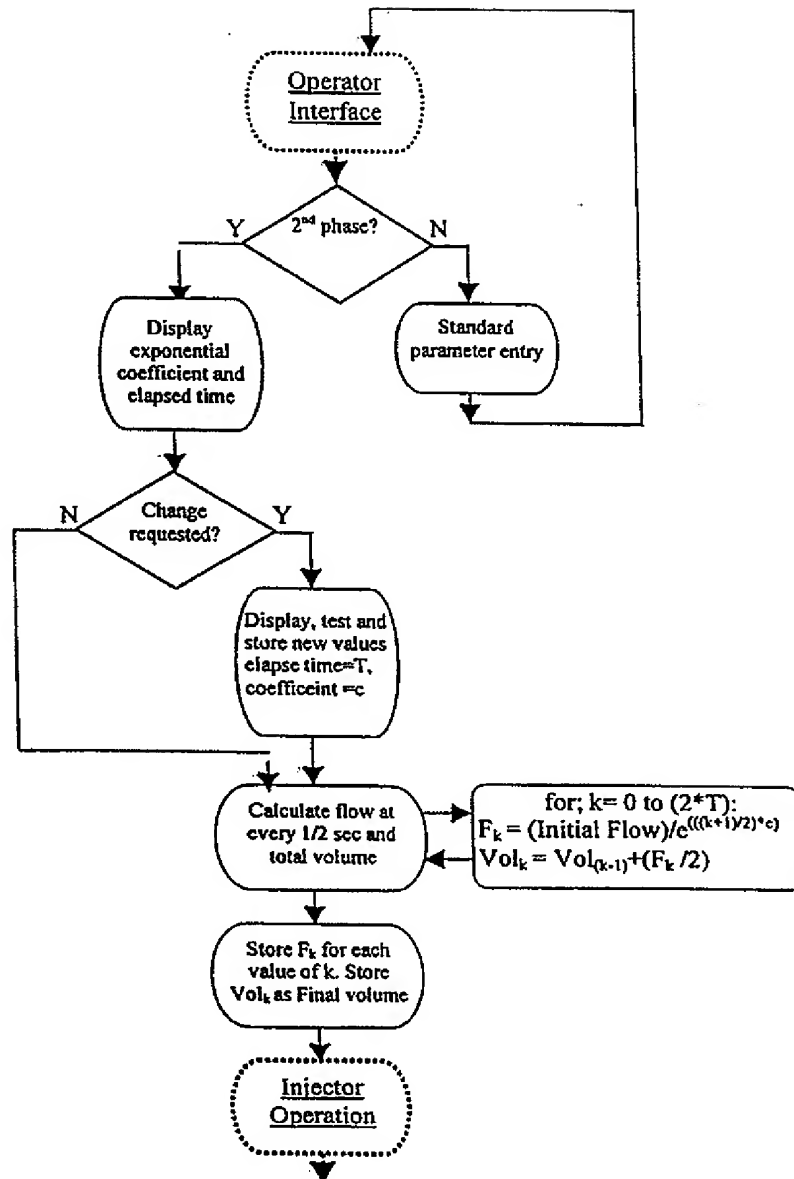
$$Qc(t) \cong \frac{Q\,\alpha\,(Qv\, Vs - Q\, Vv)}{Cc\, Qv\, Vs} E^{\frac{-Qt}{Vs}} = (\text{initial injection rate}) * E^{\frac{-Qt}{Vs}}. \qquad [15]$$

The parameters forming multiplication terms outside the exponential term in this equation are independent of time and normalized by normalization constant 'α' to set as the initial injection rate.

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Injector with exponentially decaying flow rate

Flow diagram of implementation (2 pages):

Operator Interface

2nd phase? — Y / N

(Y) Display exponential coefficient and elapsed time

(N) Standard parameter entry

Change requested? — N / Y

(Y) Display, test and store new values elapse time=T, coefficeint =c

Calculate flow at every 1/2 sec and total volume

for; k= 0 to (2*T):
$$F_k = (\text{Initial Flow})/e^{(((k+1)/2)*c)}$$
$$Vol_k = Vol_{(k-1)} + (F_k/2)$$

Store F_k for each value of k. Store Vol_k as Final volume

Injector Operation

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Injector with exponentially decaying flow rate
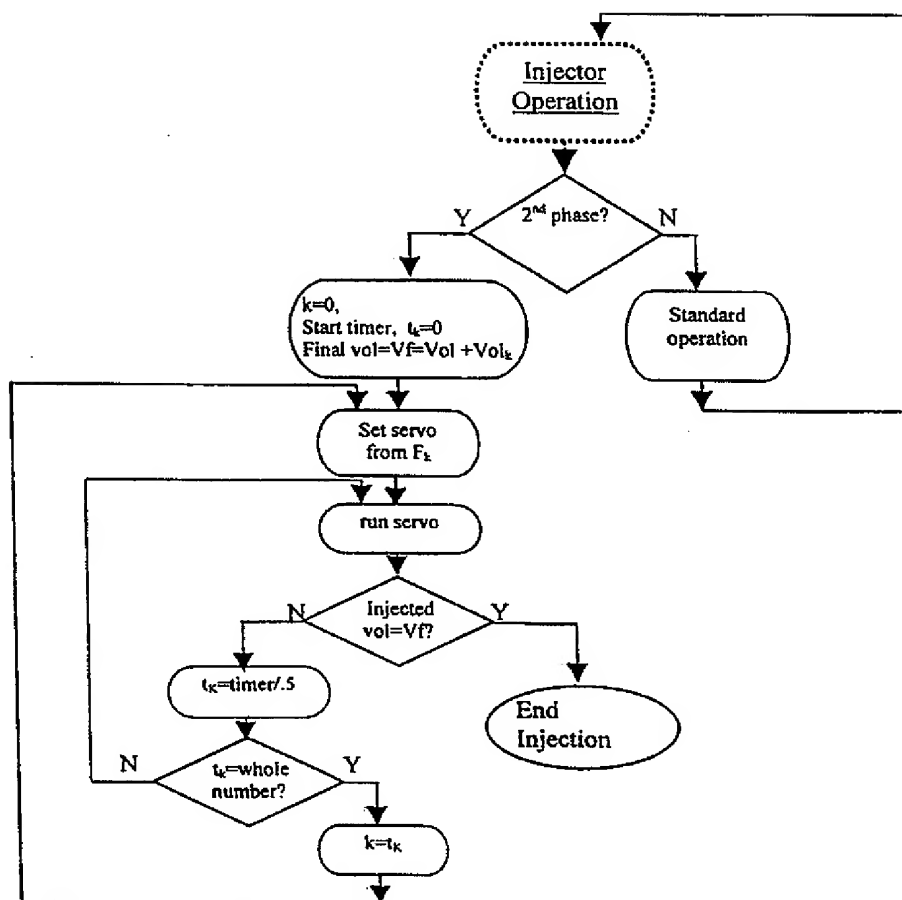
Injector with exponentially decaying flow rate

File examples (10 pages)
(Note: Additions to code are shown in bold)

```
int tybreak,tyflow[300],tyspeed[300],tytime;
float tyramp;
/*********************************************************
 *
 * Highlights the phase that is currently running and displays current phase
 * injection parameters.
 *
 *
 */
void PhaseTo(byte style,byte phase)
{
int i, index;

i = (phase >= 1) ? phase - 1 : 0;

sprintf(parm_line[(i*4)].parmpos,"%1.1d",i+1);
if (i==1)
    sprintf(parm_line[(i*4+1)].parmpos,"%01.2f",(tyramp/*0.01*edit_parms.phase
                                                  [index].flow*/));
else
    sprintf(parm_line[(i*4+1)].parmpos,"%01.1f",(0.1*run_parms.phase[i].flow));
    sprintf(parm_line[(i*4+2)].parmpos,"%3.3d",run_parms.phase[i].vol);
if ((i == 3) || ((i < 3) && (i!=1)&& (TestRunPhase(i+1) == FALSE)))
    sprintf(parm_line[(i*4+3)].parmpos,"%1s",justablank);

else if (i==1)
    {
    sprintf(parm_line[(i*4+3)].parmpos, "%3.3d",tytime);
    tydiag(8);
    }

else
    sprintf(parm_line[(i*4+3)].parmpos, "%3.3d",run_parms.phase[i].idly);
```

Injector with exponentially decaying flow rate

```
/**********************TyPhaseParams   xty
*  Calculates  parameters for  inject by exponential delay
**
*/
 void TyPhaseParms(void)
{
 float k;
 int tytime,j;
 for (j=0;j<200;j++) tyflow[j]=1;
 tyramp=(float)run_parms.phase[1].flow*.01;
 run_parms.phase[1].flow=run_parms.phase[0].flow;
 tytime=run_parms.phase[1].idly;
 run_parms.phase[1].vol=0;
 for (j=0;j<=2*tytime;)
     {
       k=(float)((j+1)/2);
       tyflow[j]=(int)(((float)run_parms.phase[1].flow/exp(k*tyramp))+0.5);
       run_parms.phase[1].vol+=(int)((float)tyflow[j]/2);
       if (tyflow[j] < 1 ) tyflow[j]=1;
       tyspeed[j] = (int)(((float)ref_period / (float)tyflow[j])+0.5);
       switch (tyflow[j])    /*set the rate multiplier for low speed */
             {
               case 1: ratemult =0.60; break;
               case 2: ratemult =0.85; break;
               default: ratemult = 1.0; break;
               }
        tyspeed[j] = (unsigned int)(tyspeed[j] * ratemult);
        j++;
        }
      run_parms.phase[1].vol=run_parms.phase[1].vol/10;
      servo_data[1].phase_delay=0;
      brakecomp=0;
      servo_data[1].speedx=tyspeed[0];
      run_parms.phase[1].flow=tyflow[0];
      DisplayRunParms();
      run_parms.phase[1].idly=0;

    if (j=GetRunProgVol() > syringe_vol)
      {
       EnableLamp(OFF);
       ChangeStateTo(OVERRIDE);
       }
 }
```

Injector with exponentially decaying flow rate

```
/***** CalcPhaseParms *******************************************************
 *
 * Calculate the parameters for the SERVO task based on the previous destination
 * position.
 *
 * Input: void
 * Return: void
 * Called By: MonitorInjection
 *
 */

void CalcPhaseParms(void)
{
int i;
brakecomp = 0;
for (i = 0; (i < MAX_PHASES) && (run_parms.phase[i].validity); i++)
    {
    brakecomp = (run_parms.phase[i].flow * run_parms.phase[i].flow) / 60;
    if (i == 0)
        servo_data[0].destpos = encoder_cnt - (run_parms.phase[0].vol * cnts_per_ml)
+ brakecomp;
        else if (i==1)
            {
            TyPhaseParms();
            brakecomp=0;
            servo_data[i].destpos = servo_data[0].destpos - (run_parms.phase[1].vol *
                                                             cnts_per_ml) + brakecomp;
            }
    }

i = GetRunProgVol();
vol_check = (ph_atod - (i * atod_factor)) - 3;
}
```

Injector with exponentially decaying flow rate

```
/***** TestRunPhase ***************************************************
*
* This will test the validity of a given phase in the run parameters.
*
* Input: phase number
* Return: TRUE | FALSE   where TRUE = valid
* Called By: DisplayRunParms
*
*/

int TestRunPhase(int i)
{
if (((run_parms.phase[i].vol == 0) && (i!=1))|| (run_parms.phase[i].flow == 0))
    return (FALSE);
else
    return (TRUE);
}
```

Injector with exponentially decaying flow rate

```
/**** DisplayRunParms ********************************************************
*
* Display the injection parameters currently in "run_parms". If this isn't a valid
* injection, then this function should not have been called, eventually this will cause
* an error or warning. This should only be called from the "start_inj" state.
*
* It is assumed that there is some set of parameters already displayed.
*
* Input: void
* Return: void
* Called By: StartInjection
*
*/

void DisplayRunParms(void)
{
int injvol;
byte index;

InitMainLines();          /* blank out the main window buffer */

DrawStrings(10,parmlabels);
```

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```c
for (injvol = 0,index = 0; index < MAX_PHASES; index++)
{
    if (run_parms.phase[index].validity)
    {
        sprintf(parm_line[((index*4)].parmpos, "%1.1d",index+1);
        if(index==1)
            sprintf(parm_line[((index*4+1)].parmpos, "%01.2f",
                    (tyramp/*0.01*edit_parms.phase[index].flow*/);
        else
            sprintf(parm_line[((index*4+1)].parmpos, "%01.1f",
                    (0.1*run_parms.phase[index].flow));
        sprintf(parm_line[((index*4+2)].parmpos, "%3.3d",run_parms.phase[index].vol);

        if ((index == 3) || ((index < 3) && (index!=1) && (TestRunPhase(index+1) ==
                                                           FALSE)))
        {
            sprintf(parm_line[((index*4+3)].parmpos, "%1s",justablank);
        }
        else
            sprintf(parm_line[((index*4+3)].parmpos, "%3.3d",run_parms.phase[index].idly);
        injvol += run_parms.phase[index].vol;
    }
}
```

Injector with exponentially decaying flow rate

```
int TestPhase(int i)
{
if (((edit_parms.phase[i].vol == 0) && (i!=1)) || (edit_parms.phase[i].flow == 0) )
    return (FALSE);
else
    return (TRUE);
}

void ValidSetClr(void)
{
short i,vol,flow;
for (i = 0; i < MAX_PHASES; i++)              /* check the validity of each phase */
    {
    vol = edit_parms.phase[i].vol;      /* get the volume and flow values for the phase */
    flow = edit_parms.phase[i].flow;    /* if the values are in range */
    if (((vol > 0)||(i==1&&vol==0)) && (vol <= 200) && (flow > 0) && ((flow <=
                            FLOW_MAX_200)||(i==1&&flow<=99)))
        edit_parms.phase[i].validity = 0xff;
    else
        edit_parms.phase[i].validity = 0;        /* ...else, indicate invalid */
    }
}
```

Injector with exponentially decaying flow rate

```
void ActiveParmTo(byte style)
{
byte i, j;
j = (b_phs_pnt - 1);
i = j * 4;

if (b_phs_pnt==2)
  sprintf(parm_line[(i+1)].parmpos, "%01.2f",(0.01*edit_parms.phase[j].flow));
else
  {
  sprintf(parm_line[(i+1)].parmpos, "%01.1f",(0.1*edit_parms.phase[j].flow));
  sprintf(parm_line[(i+2)].parmpos, "%3.3d",edit_parms.phase[j].vol);
  sprintf(parm_line[(i+3)].parmpos, "%3.3d",edit_parms.phase[j].idly);
  sprintf(parm_line[16].parmpos, "%3.3d",edit_parms.sdly);

if (active_parm == SDLY_KEY)          /* if active parm is scan delay */
  {
  i = 16;                             /* ...then it's at a fixed location in parm_line */
  DrawString(10,font_type_4);         /* ...and it uses a smaller font size */
  }
else
  {
  i += (active_parm+1);               /* ...else get the active parameter (add 1 to bypass
phase #) */
  DrawString(10,font_type_5);         /* ...and use a larger font size */
  }

TextStyle(style);                     /* output the active parameter in the selected style */
DrawString(10,parm_line[i].parmstart);
DrawString(10,parm_line[i].parmpos);
DrawString(10,font_type_4);
DrawString(10,style_plain);
}
```

Injector with exponentially decaying flow rate

```
void DoActiveParm(int direction,int count)
{
ainjd = edit_parms.phase[b_phs_pnt-1].idly;    /* load inject delay */
avol  = edit_parms.phase[b_phs_pnt-1].vol;     /* load volume */
aflow = edit_parms.phase[b_phs_pnt-1].flow;    /* load flow rate */

switch(active_parm)       /* the active_parm value is set in PEMODE when a key ispressed*/
    {
    case IDLY_KEY:   if (direction == INCREMENT)
                        ainjd = (ainjd < (INJD_MAX-(INJD_DELTA*count))) ?
                                ainjd+(INJD_DELTA*count)  :  INJD_MAX;
                     else
                        ainjd = (ainjd < (INJD_DELTA*count)) ? 0 : ainjd-
                                                              (INJD_DELTA*count);

                     break;

    case FLOW_KEY:   if (direction == INCREMENT)
                     {
                     if (b_phs_pnt==2)
                        aflow = (aflow < (99-(FLOW_DELTA*count))) ?
                                           aflow+(FLOW_DELTA*count)  : 99;
                     else
                        aflow = (aflow < (flow_max-(FLOW_DELTA*count))) ?
                                           aflow+(FLOW_DELTA*count)  : flow_max;
                     }
                     else
                        aflow = (aflow < (FLOW_DELTA*count)) ? 0 : aflow-
                                                              (FLOW_DELTA*count);

                     break;
```

```
case  VOL_KEY:

        if (direction == INCREMENT)
            avol = (avol < (max_ph_vol-(VOL_DELTA*count))) ?
                    avol+(VOL_DELTA*count) : max_ph_vol;

        else
            avol = (avol < (VOL_DELTA*count)) ? 0 : avol-(VOL_DELTA*count);
        break;

case  SDLY_KEY:

        if (direction == INCREMENT)
            edit_parms.sdly=(edit_parms.sdly<(SCAN_MAX-(SCAN_DELTA*count))) ?
                    edit_parms.sdly+(SCAN_DELTA*count) : SCAN_MAX;

        else
            edit_parms.sdly = (edit_parms.sdly < (SCAN_DELTA*count)) ? 0 :
                    edit_parms.sdly-(SCAN_DELTA*count);

        break;
    }

edit_parms.phase[b_phs_pnt-1].idly = ainjd;       /* store inject delay */
edit_parms.phase[b_phs_pnt-1].vol = avol; /* store volume */
edit_parms.phase[b_phs_pnt-1].flow = aflow;       /* store flow rate */
```

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Injector with exponentially decaying flow rate

```
for (injvol = 0, index = 0; index < MAX_PHASES; index++)
{
if (edit_parms.phase[index].validity)
    {
    sprintf(parm_line[(index*4)].parmpos, "%1.1d",index+1);
    if (index==1)
    sprintf(parm_line[(index*4+1)].parmpos, "%01.2f",
                       (0.01*edit_parms.phase[index].flow));
    else
    sprintf(parm_line[(index*4+1)].parmpos, "%01.1f",
                       (0.1*edit_parms.phase[index].flow));

    sprintf(parm_line[(index*4+2)].parmpos, "%3.3d",
                       edit_parms.phase[index].vol);


    if ((index == 3) || ((index < 3) && (index!=1) &&
                       (TestPhase(index+1) == FALSE) &&
                       (new_state!=EDINJ)))
    sprintf(parm_line[(index*4+3)].parmpos, "%1s",justablank);
    else
    sprintf(parm_line[(index*4+3)].parmpos, "%3.3d",
                       edit_parms.phase[index].idly);

    injvol += edit_parms.phase[index].vol;
```

Injector with exponentially decaying flow rate

```
extern void tydiag(int);
unsigned short servo_state_key;              * V1.16 servo variable to indicate PH relay i open*/
extern int SetTySpeed(int);
int tycnt,tysec;  extern int tytime,tyflow[],tyspeed[];
/***** Servo
**********************************************************************
*
* This is servo controller task. It is responsible for controlling the PWM and brake
* circuits to produce the desired velocity and distance movements as required by an
* injection, fill or purge command.
*
*/
unsigned short lcheck_value,lcheck_value2;

void Servo(void)
{
int i,j;
short a;
tycnt=tysec=0;

while(TRUE)
    {
```

```
_clrevt(RUN_SERVO);                    /* ensure that the servo isn't told to run yet */
_wteset(RUN_SERVO);                    /* wait till I'm told to move */

while ((servo_flags.stop == 0) && (fault_buffer[0] == 0))
{
    U2SETOPB = 0x40;    /* use to measure time in servo loop */

    ToggleFailSafe();    /*    toggle failsafe on DS1239 */
    CheckServoOK();

    p_index++;                          /* increment phase time counter */
    if ((phs_pnt==2)&&(p_index % 21==0))
    {
        tysec=(p_index/21);

        run_parms.phase[1].flow=tyflow[tysec];
        servo_data[1].speedx =tyspeed[tysec];
    }

    if (run_time == (servo_data[phs_pnt-1].start_time + risetime))
                         servo_data[phs_pnt-1].rise_count = encoder_cnt;
    if (start_timing == TRUE)            /* if it's OK to start timing i.e.
                                            seen.encoder counts */
    {
        run_time++;       /* ...increment complete injection counter */

    if ((run_parms.phase[phs_pnt-1].flow <= 5) && !fill_hold &&
                        !doing_auto && (calib_press == CALIBRATED))
        (
```

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Injector with exponentially decaying flow rate

```
                sec_cnt = p_index / 43;
                sec_trip = p_index % 43;
                if (!sec_trip)
                    {
                    if (((servo_data[phs_pnt-1].start_count-
                          encoder_cnt)/sec_cnt) < onesec_cnt)
                                               /* if too slow */
                        if (ratemult > 0.85)
                            ratemult -= 0.01;

                        }                        /* if too fast */
                    else
                        {
                        if (ratemult < 1.15) ratemult += 0.01;
                        }
                    servo_data[phs_pnt-1].speedx =
                            (unsigned int)(start_speed * ratemult);

                    }

                }

            StopServo(3);        /* always stop when exiting the control loop */

            }

        StopServo(7);        /* just in case we exit the positioning loop without stopping */
        while (TRUE)         /* if we somehow terminate the infinite loop, then sit here
                                                                    forever */;

    }
```

$= 1,2..40$ $.a = .026$ $.40$

$= 1,2..40$ $.v \quad \int_{.0}^{.} 2 \cdot e^{.a \cdot t} dt \quad .v = 49.734$

$._t = 2 \cdot e^{-a \cdot t} \quad .v_t = \sum_{t=1}^{t} f_{t-1}$

$.V_t = 198 - v_t$

|	$.f_t$	$.v_t$	$.V_t$
1	1.949	0	198
2	1.899	1.949	196.051
3	1.85	3.847	194.153
4	1.802	5.697	192.303
5	1.756	7.5	190.5
6	1.711	9.256	188.744
7	1.667	10.967	187.033
8	1.624	12.634	185.366
9	1.583	14.259	183.741
10	1.542	15.841	182.159
11	1.503	17.383	180.617
12	1.464	18.886	179.114
13	1.426	20.35	177.65
14	1.39	21.776	176.224
15	1.354	23.166	174.834
16	1.319	24.52	173.48
17	1.285	25.84	172.16
18	1.253	27.125	170.875
19	1.22	28.378	169.622
20	1.189	29.598	168.402
21	1.159	30.787	167.213
22	1.129	31.946	166.054
23	1.1	33.074	164.926
24	1.072	34.174	163.826
25	1.044	35.246	162.754
26	1.017	36.29	161.71
27	0.991	37.307	160.693
28	0.966	38.298	159.702
29	0.941	39.264	158.736
30	0.917	40.205	157.795
31	0.893	41.122	156.878
32	0.87	42.015	155.985
33	0.848	42.885	155.115
34	0.826	43.733	154.267
35	0.805	44.56	153.44
36	0.784	45.365	152.635
37	0.764	46.149	151.851
38	0.745	46.913	151.087
39	0.726	47.658	150.342
40	0.707	48.384	149.616

Flow vs time
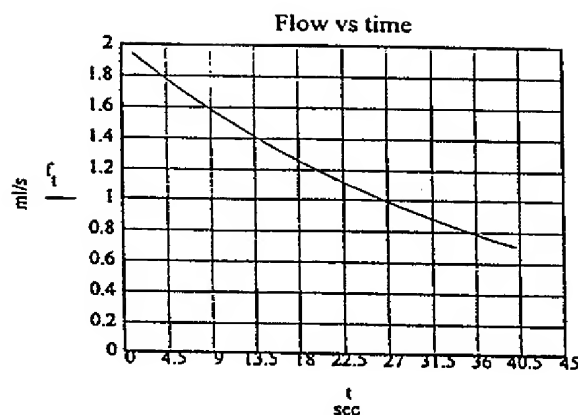
.Validation:
To validate the injector, the syringe volume vs time was
measured during an injection, using a linear position transducer.
This measurement is shown on the following page as a plot of
volume vs time.
This plot was compared against the calculated volume also shown
on the following page.

Syringe volume vs time (start at 200ml)
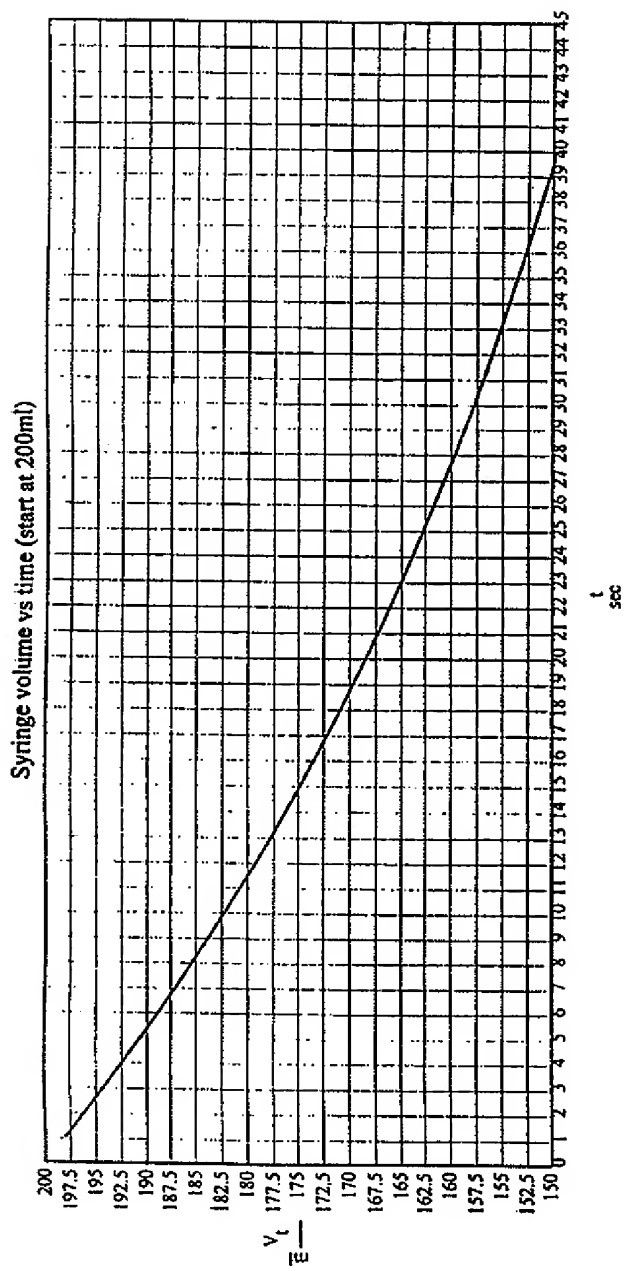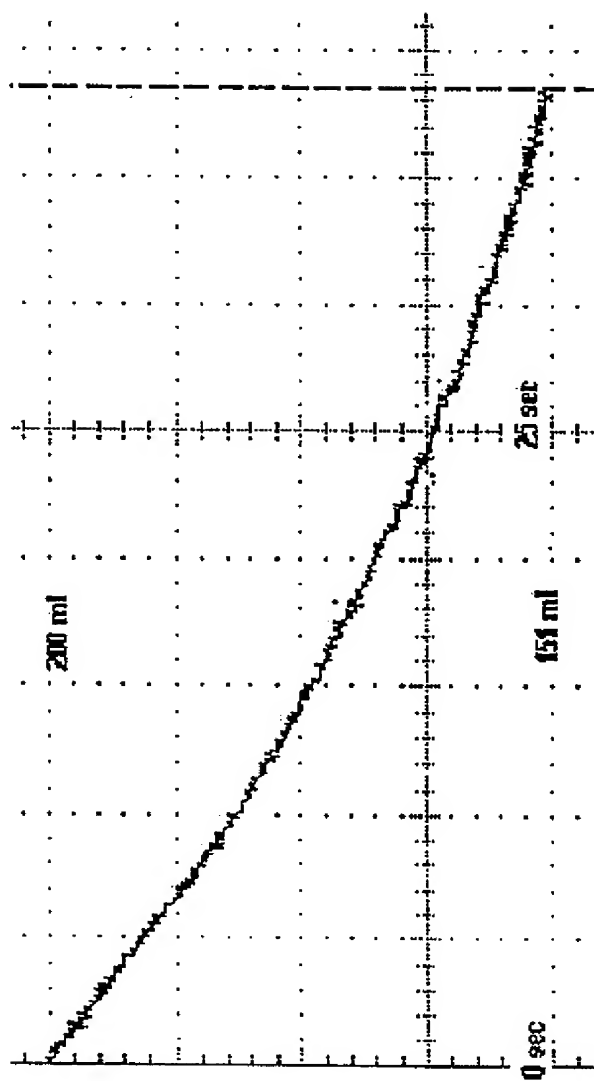
What is claimed is:

1. A contrast injector for injecting a patient with a contrast agent to substantially achieve a desired level of vascular enhancement during a desired interval of an injection routine comprising a rate control for controllably reducing the injection rate during said desired interval of said injection routine in order to substantially maintain said desired level of vascular enhancement.

2. The contrast injector of claim 1 wherein said rate control includes a control for ramping the injection rate during an injection routine.

3. The contrast injector of claim 2 wherein said rate control includes a control for continuously ramping the injection rate during an injection routine.

4. The contrast injector of claim 3 wherein said rate control includes a control for continuously ramping the injection rate at substantially an exponential rate having a decay coefficient approximating a selected cardiac output per body weight typifying the patient.

5. The contrast injector of claim 3 wherein said rate control includes a control for continuously ramping the injection rate at a substantially linear approximation of an exponential function having as its decay coefficient a value directly proportional to a cardiac output per body weight typifying the patient.

6. The contrast injector of claim 4 wherein said rate control is software programmable.

7. The contrast injector of claim 6 wherein said rate control comprises a software programmable microprocessor.

8. The contrast injector of claim 7 further comprising an input device for an operator to input various patient parameters for use by said software in calculating the exponential rate.

9. The contrast injector of claim 1 wherein said rate control includes a software controlled microprocessor, and an input device for an operator to input various patient parameters for use by said software in calculating substantially an exponential rate, said controlled reduction being at said calculated substantially exponential rate.

10. A microprocessor controlled contrast injector for injecting a patient with a contrast agent to achieve and

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substantially maintain a desired level of vascular enhancement, said injector comprising a software programmed microprocessor for controlling the injection rate, an operator input device allowing for input of various patient parameters for use by said software in determining said injection rate, and said software configured to provide controlled reduction of said rate over a substantial portion of an injection routine.

11. The injector of claim 10 wherein said software provides for ramped reduction over a substantial portion of the injection routine.

12. The injector of claim 11 wherein said software provides for reduction at an exponential rate over a substantial portion of the injection routine.

13. The injector of claim 12 wherein said exponential rate has a decay coefficient corresponding to a selected cardiac output per body weight typifying the patient.

14. The injector of claim 11 wherein said ramped reduction is at a rate equal to a substantially linear approximation of an exponential function having as its decay coefficient a value directly proportional to a cardiac output per body weight typifying the patient.

15. In a contrast injector, the improvement comprising a software programmed microprocessor configured to provide for an injection routine comprising an initial injection rate followed by an exponentially decaying injection rate having a decay coefficient approximating a selected cardiac output per body weight typifying a patient.

16. The contrast injector of claim 15 further comprising an input device for operator input of various patient parameters, said software being configured to adjust said decay coefficient in response to at least some of said various patient parameters.

17. In a contrast injector, the improvement comprising a software programmed microprocessor configured to provide for an injection routine comprising an initial injection rate followed by a controlled ramped reduction of said injection rate sufficient to maintain a desired level of enhancement.

18. The contrast injector of claim 17 wherein said ramped reduction is at a varying rate.

19. The contrast injector of claim 18 wherein said ramped reduction is at a controllable rate.

20. The contrast injector of claim 17 wherein said ramped reduction is at a rate calculated to be adequate to substantially maintain a minimal vascular enhancement.

21. A contrast injector for injecting a patient with a contrast agent to substantially achieve a desired level of vascular enhancement during a desired interval of an injection routine comprising a rate control configured for implementing a multiphasic injection protocol.

22. The contrast injector of claim 21 wherein said multiphasic injection protocol has an exponential decay coefficient approximating 0.01.
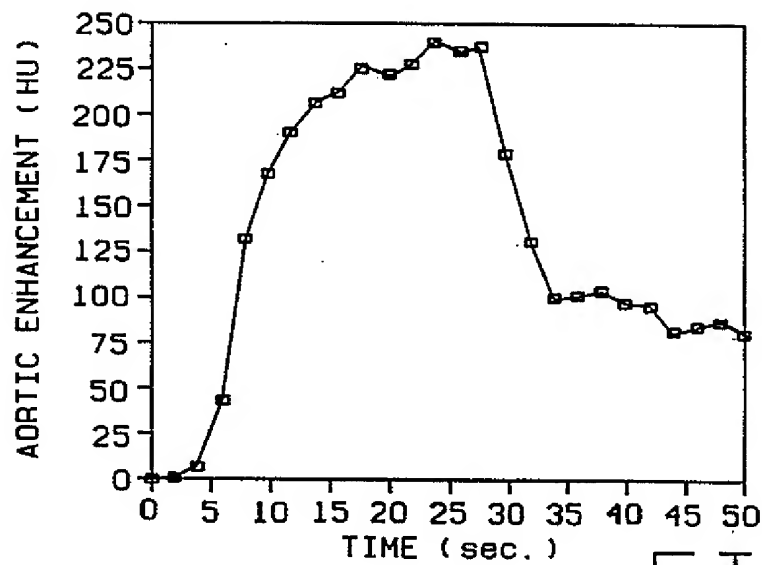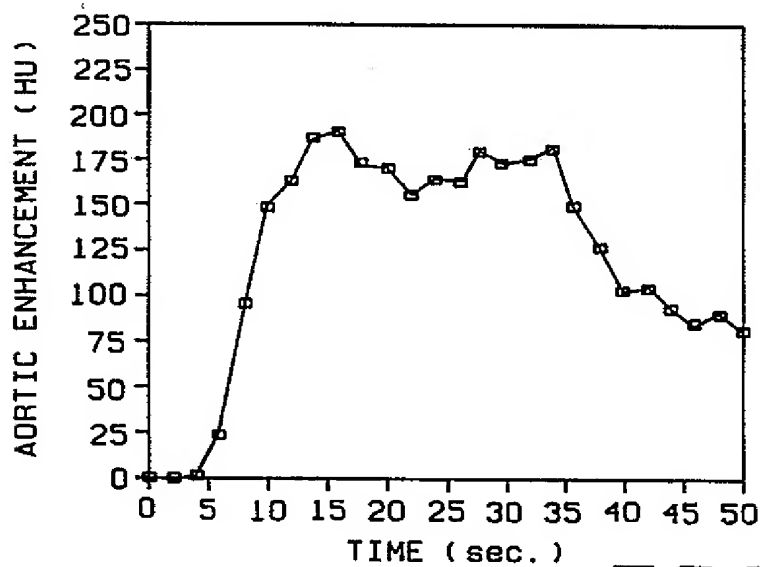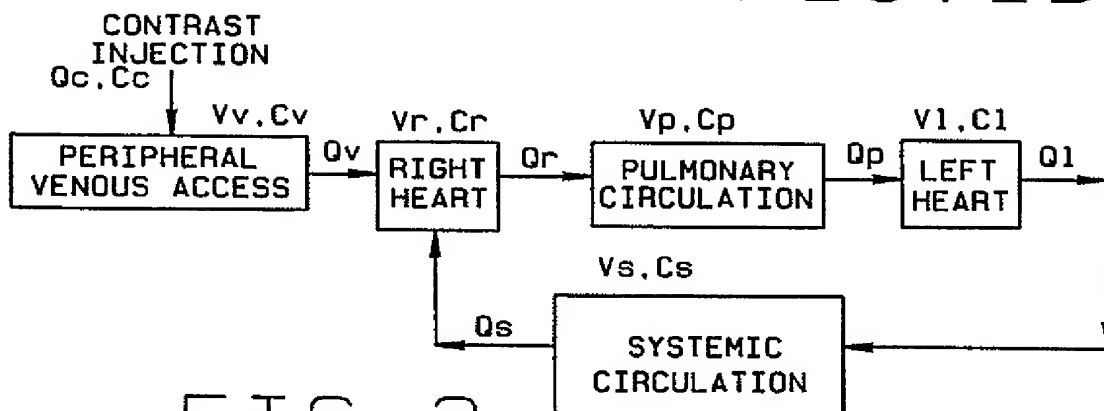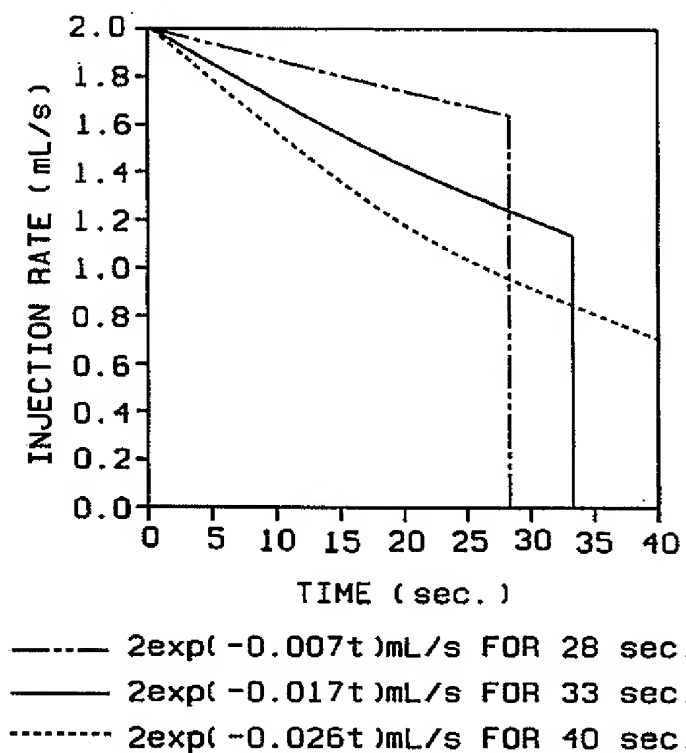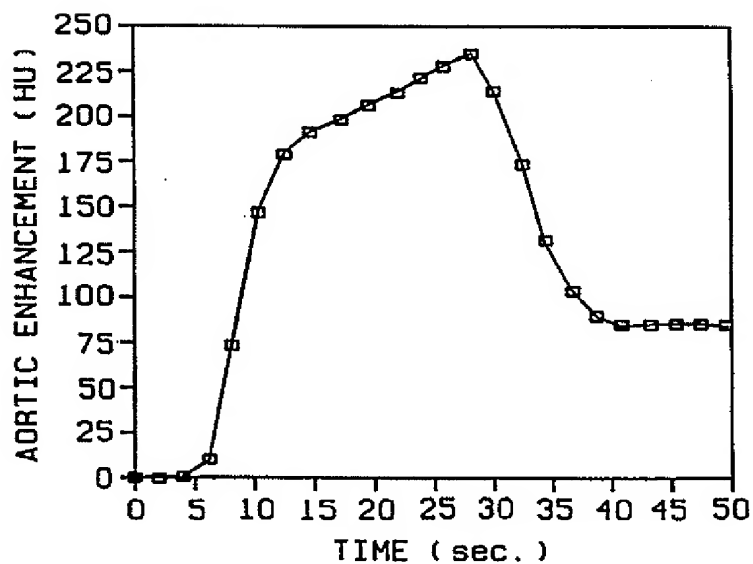
FIG.1A

FIG.1B

FIG.2

FIG.3

FIG.4

FIG.5A

FIG.5B

FIG.6

- - - - - 3mL/S FOR 53 sec.
———— 3exp(-0.01)mL/s
          FOR 77 sec.

FIG.7

- - - - - 40% DECREASE IN C.O.
—·—·— 20% DECREASE IN C.O.
———— NORMAL C.O.

FIG.8A

—*— 2exp(-0.007t)mL/s
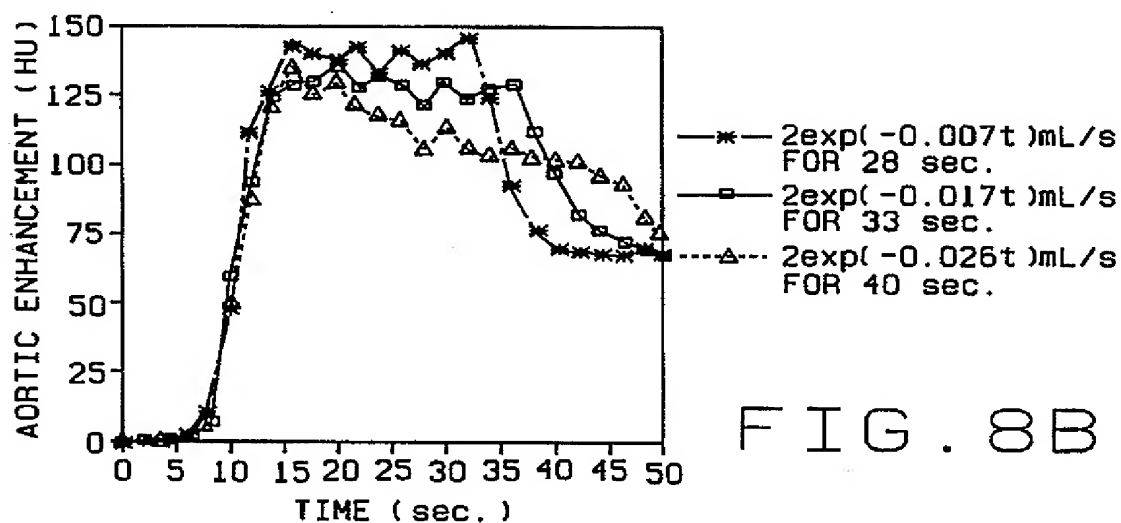   FOR 28 sec.
—□— 2exp(-0.017t)mL/s
          FOR 33 sec.
--△-- 2exp(-0.026t)mL/s
          FOR 40 sec.
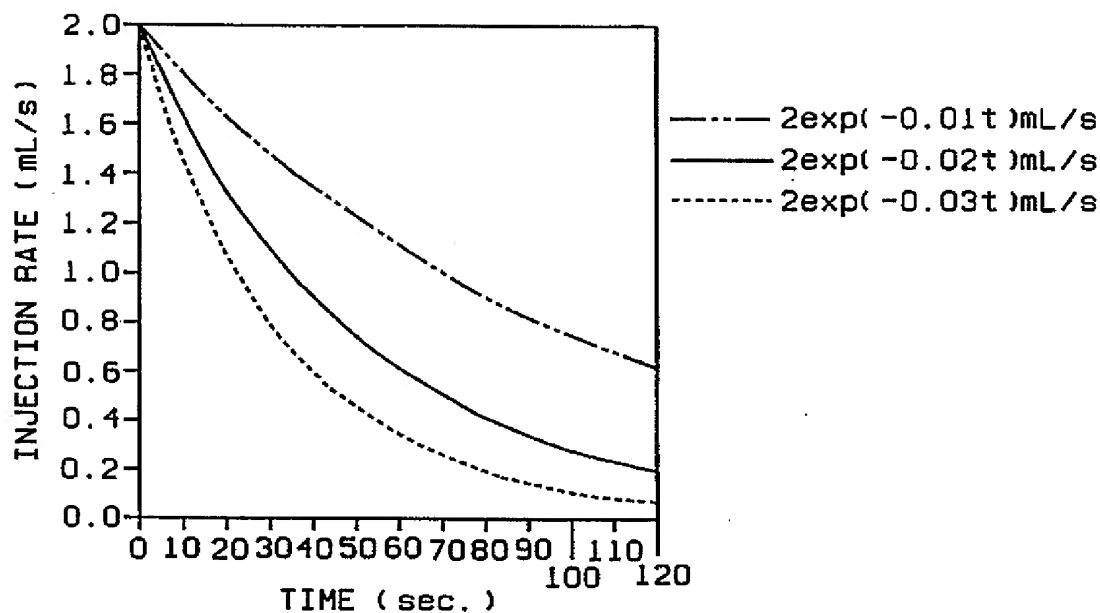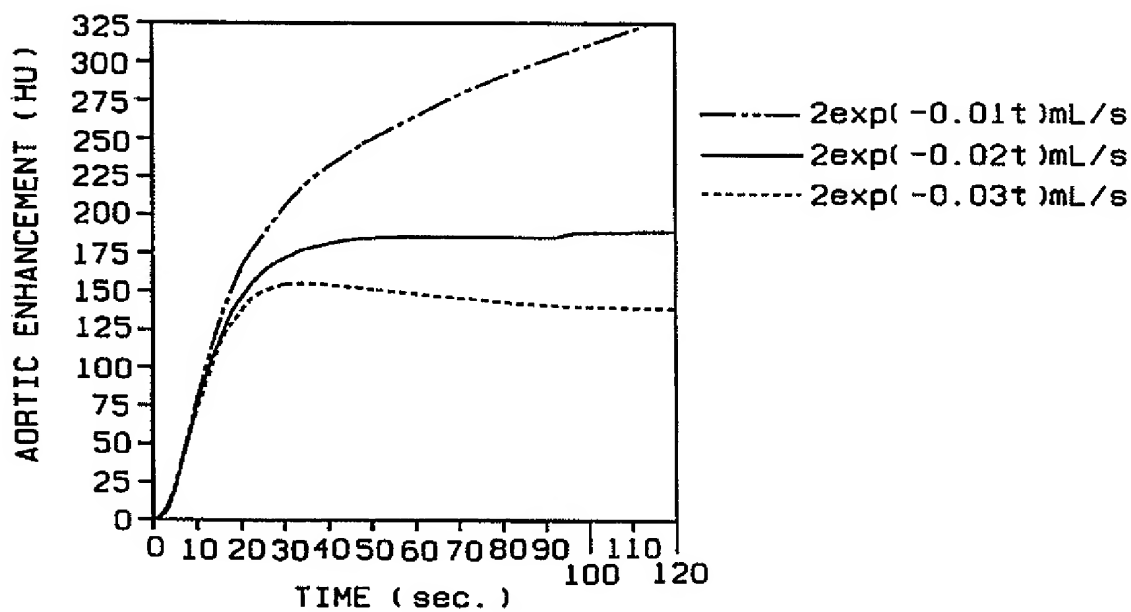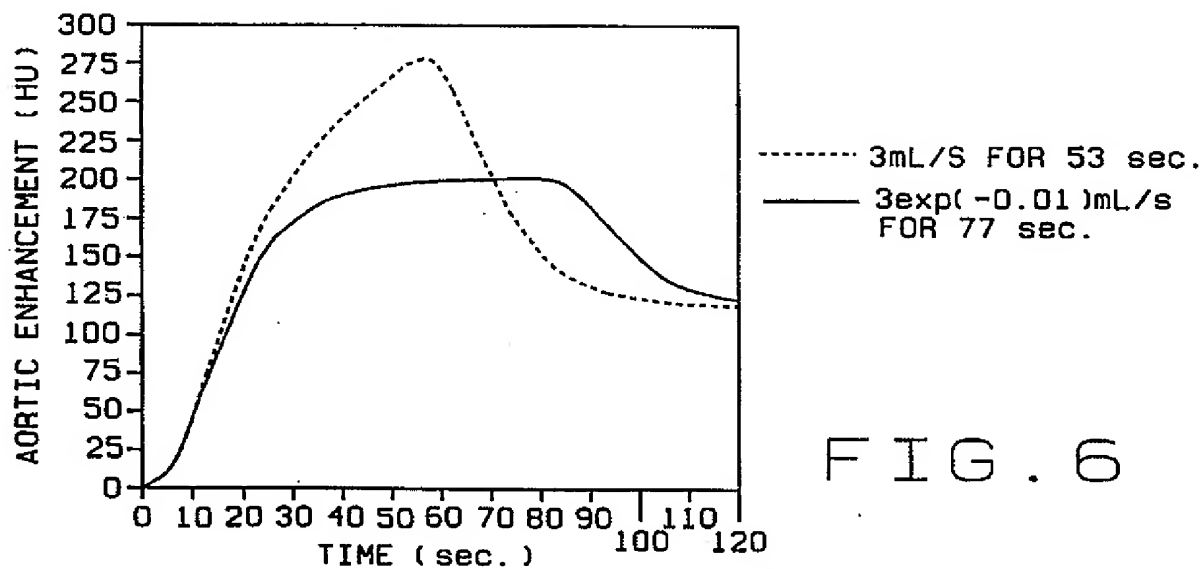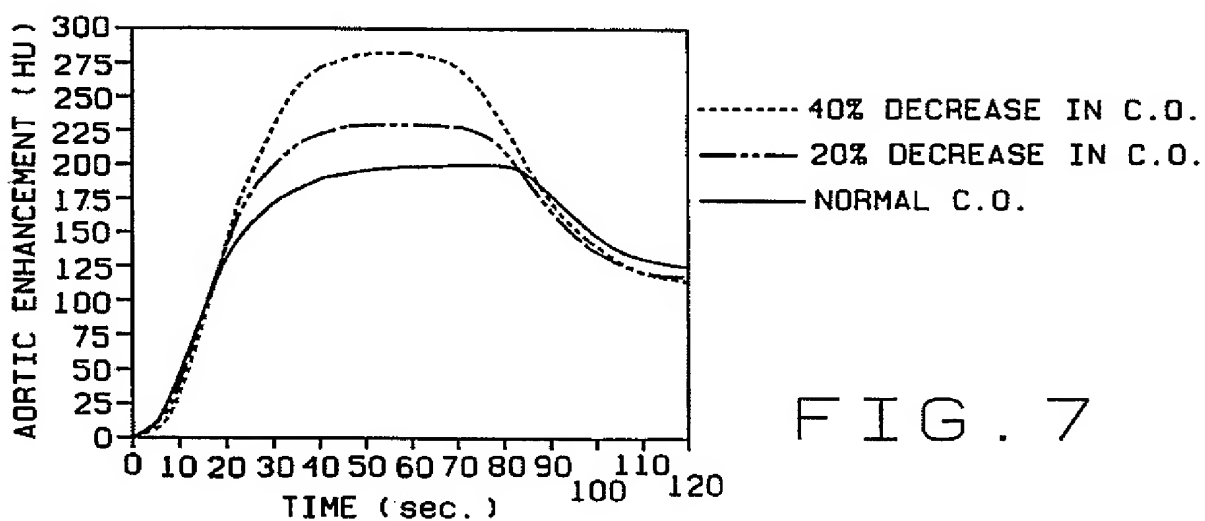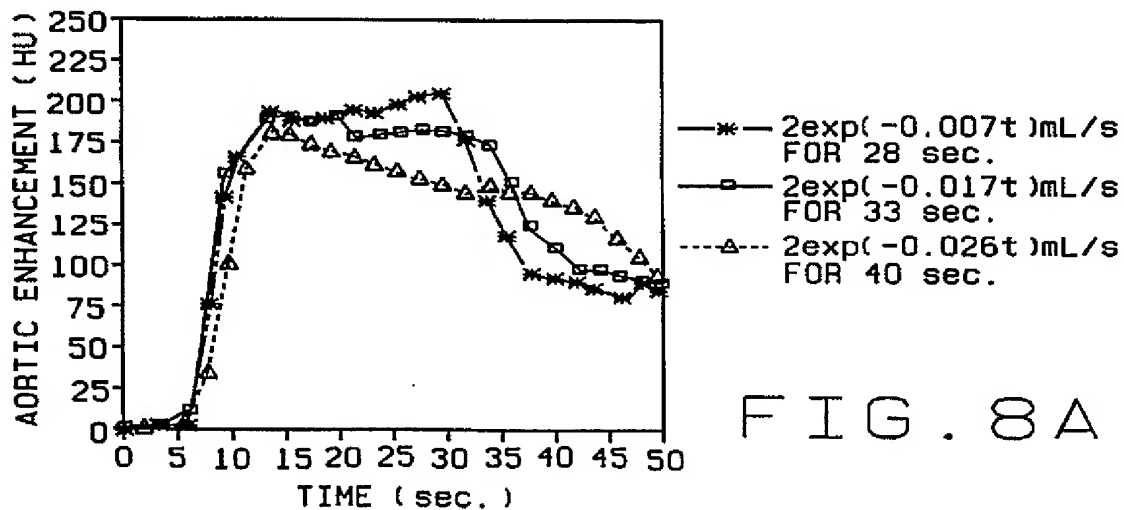
FIG.8B
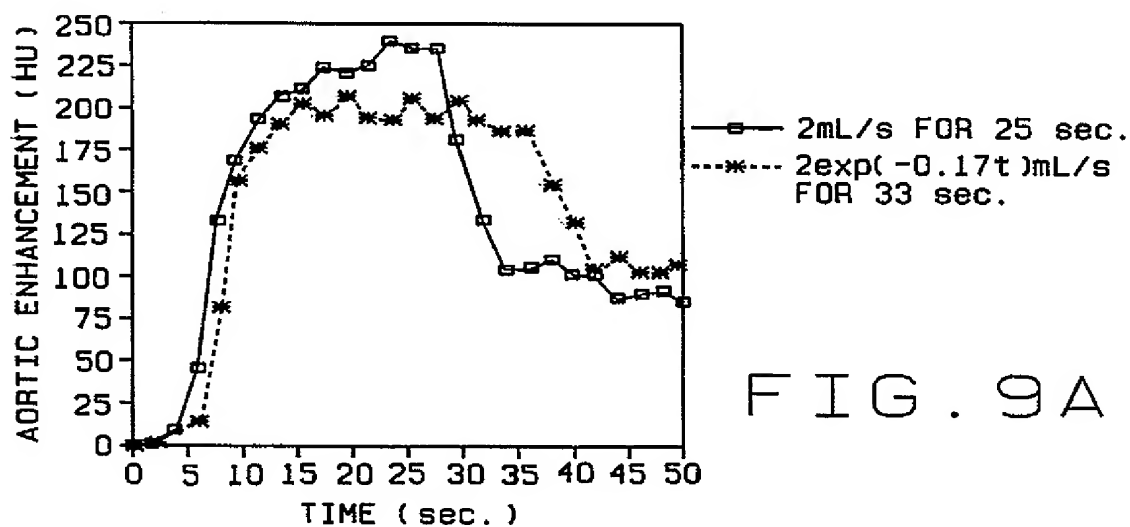
FIG.9A
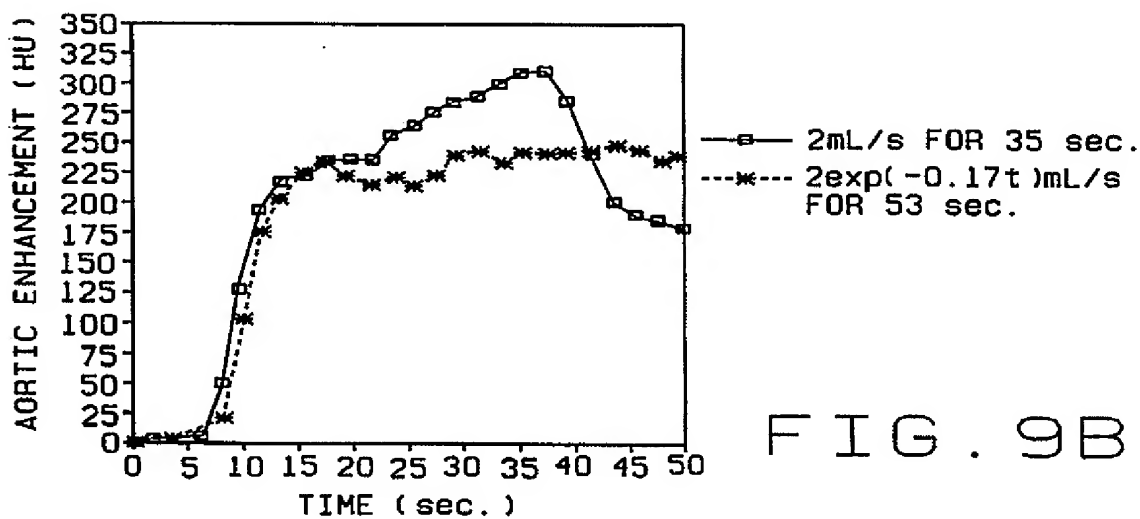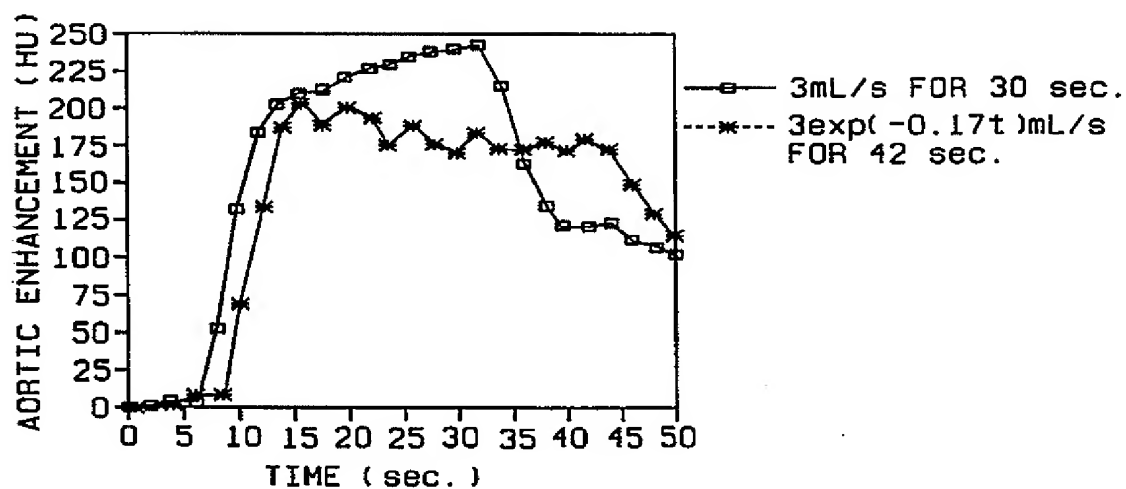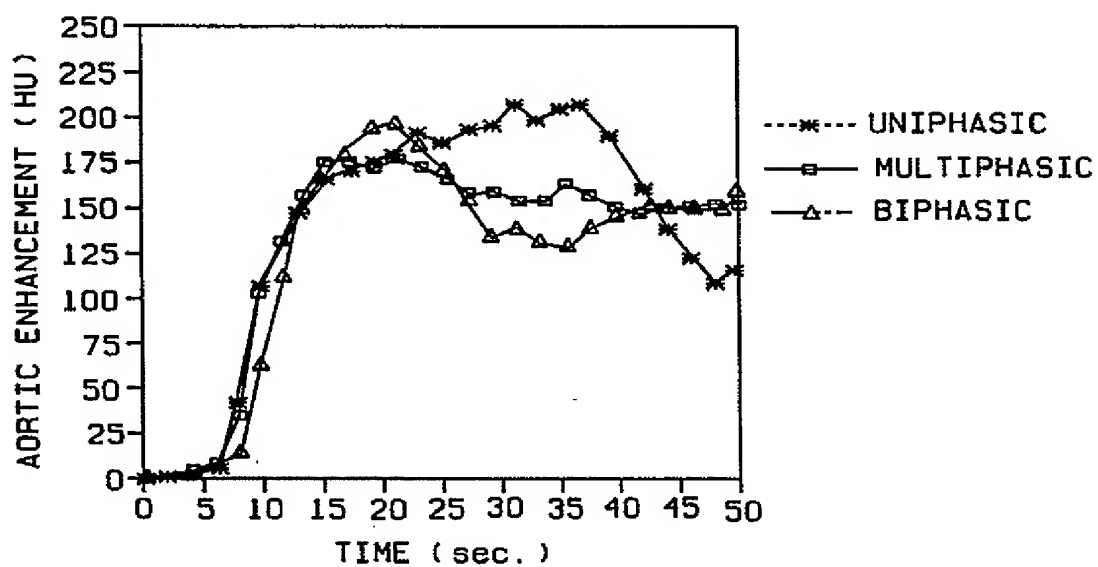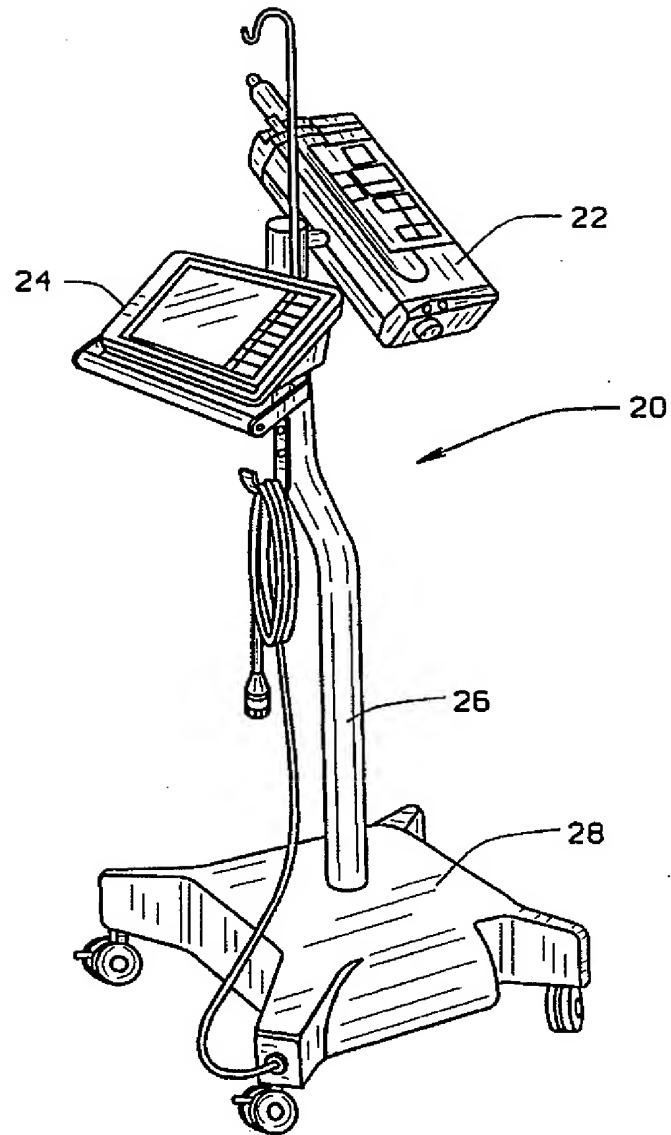

FIG.9B

FIG.10A

FIG.10B

FIG.11

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/09577

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61M 37/00
US CL :604/131

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/48, 65, 67, 131, 890.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,812,724 A (LANGER et al.) 14 March 1989, entire patent, especially Abstract.	1-22
X	US 5,687,208 A (BAE et al.) 11 November 1997, entire patent, especially claims 17-30.	1-22
A	US 5,583,902 A (BAE) 10 December 1996, entire patent.	1-22
A	US 4,006,736 A (KRANYS et al.) 08 February 1977, entire patent.	1-22
A	US 4,695,271 A (GOETHEL) 22 September 1987, entire patent.	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	
"E"	earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	
		"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	
"P"	document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 JULY 2000	2 4 AUG 2000

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	JEREMY THISSELL
Facsimile No. (703) 305-3230	Telephone No. (703) 305-5261

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